Spinal cord injury is associated with an increased risk of atrial fibrillation: A population-based cohort study

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BACKGROUND Spinal cord injury (SCI) can result in substantial sensorimotor and autonomic dysfunctions and an adverse prognosis. Cardiovascular disease is the leading cause of death in patients with chronic SCI.

OBJECTIVE We conducted a retrospective cohort study to investigate the association between atrial fibrillation (AF) and SCI.

METHODS Using the National Health Insurance Research Database, we identified 41,691 patients without a history of AF who were newly hospitalized for SCI between 2000 and 2011. The comparison group included 166,724 patients without AF or SCI who were matched to the SCI group according to age, sex, and index year at a ratio of 4:1. Both cohorts were followed up until the end of 2011, and the cumulative incidence of AF was calculated. Univariate and multivariate Cox proportional hazards regression models and Kaplan-Meier curve analysis were used to compare differences in the cumulative incidence of AF between the 2 groups.

RESULTS During the mean follow-up periods of 5.69 years for the SCI group and 6.17 years for the non-SCI group, the overall incidence rates were 2.70 and 1.99 cases per 1000 person-years, respectively (crude hazard ratio 1.36; 95% confidence interval 1.24–1.48). After adjusting for age, sex, and all comorbidities, the risk of AF remained significantly higher in the SCI group than in the non-SCI group (adjusted hazard ratio 1.28; 95% confidence interval 1.17–1.40).

CONCLUSION SCI is associated with an increased risk of AF in a long-term follow-up period.

KEYWORDS Atrial fibrillation; Spinal cord injury; Cardiac arrhythmia

ABBREVIATIONS **AF** = atrial fibrillation; **CAD** = coronary artery disease; **CHF** = congestive heart failure; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **C-spinal injury** = cervical spinal injury; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Disease, Ninth Revision, Clinical Modification*; **L-S-Co-spinal injury** = lumber, sacral, coccygeal spinal cord injury; **NHI** = National Health Insurance; **NHIRD** = National Health Insurance Research Database; **PWD** = P-wave dispersion; **SCI** = spinal cord injury; **T-spinal injury** = thoracic spinal injury; **Th1** = first thoracic bertebra; **Th4** = fourth thoracic vertebra; **Th5** = fifth thoracic vertebra

Introduction

Spinal cord injury (SCI) is a severe medical condition that can cause various motor, sensory, and autonomic dysfunctions.[1] SCI may also cause long-lasting dysfunction in several organ systems, leading to high morbidity and an adverse prognosis.[2] Cardiovascular disease is the leading cause of death in patients with SCI.[3–5] Vascular thromboembolism, acute myocardial infarction, postural hypotension, orthostatic hypotension, and cardiac arrhythmia may have been reported to occur in patients with SCI.[6–9]

Cardiac arrhythmia is frequently observed in patients with SCI and is generally considered to be caused by autonomic

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dysfunction. Because the spinal sympathetic pathways that control the heart and maintain vascular tone exit at the first thoracic vertebra to fourth thoracic vertebra (Th1-Th4) levels, an unopposed parasympathetic tone may be present at the cervical or high thoracic (above Th5) level in patients with SCI. Life-threatening bradyarrhythmia or sinus arrest requiring the implantation of a pacemaker has also been reported.[8]

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia encountered in clinical practice with a prevalence of 1.0%–2.0% in the general population, can lead to substantial morbidity, reduced quality of life, and increased mortality.[10,11] AF is a complex disease caused by multiple underlying mechanisms, including autonomic neural dysregulation. Despite the clinical significance of AF, to our knowledge, no systemic analysis of a large cohort has been conducted to investigate the association between SCI and the incidence of AF. Therefore, we conducted this retrospective cohort study, using a nationwide database, to investigate this issue.

Methods

Data source

In this retrospective cohort study, we used data from the National Health Insurance Research Database (NHIRD) of Taiwan, which contains comprehensive information on clinical visits and admissions for each insurant, including demographic data, visit dates, *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes, and prescription histories. The comprehensive National Health Insurance (NHI) program[12] was established in 1995 and provides coverage to >99% of the population of 23.7 million people. The Taiwan National Health Research Institute administers the NHIRD, and before the electronic files are released, personal identification information is encrypted to protect patient privacy. In this study, we used claims data from the Longitudinal Health Insurance Database 2000, a subset of the NHIRD that contains all medical claims data on a random sample of 1,000,000 beneficiaries of the NHI program. The Longitudinal Health Insurance Database 2000 data on sex, age, and health care costs have been proved to be representative of the all insurants. This study was approved to fulfill the condition for exemption by the Institutional Review Board of China Medical University (CMUH-104-REC2-115). The institutional review board also specifically waived the consent requirement.

Sampled participants

Patients 20 years and older who were newly hospitalized for SCI (*ICD-9-CM* codes 806 and 952) between 2000 and 2011 comprised the SCI cohort. The SCI diagnosis date was defined as the index date. We classified patients with SCI into 4 subgroups: cervical SCI (*ICD-9-CM* codes 806.0, 806.1, 952.0, and 952.00–952.09); thoracic SCI (*ICD-9-CM* codes 806.2, 806.3, 952.1, and 952.10–952.19); lumbar, sacral, and coccygeal SCI (*ICD-9-CM* codes 806.4, 806.5, 806.6, 806.7, 806.8, 806.9, 952.2, 952.3, 952.4, 952.8, and 952.9); and multilevel SCI. We excluded patients diagnosed with AF (*ICD-9-CM* codes 427.3 and 427.31); atrial flutter (*ICD-9-CM* code 427.32); supraventricular tachycardia, ventricular tachycardia, and heart block (*ICD-9-CM* codes 426–427.5 and 427.81); and pacemaker implantation before the index date. For the non-SCI cohort, we randomly selected controls at a ratio of 4:1 and frequency-matched them to patients with SCI by age, sex, and index year. The same exclusion criteria were applied to the non-SCI cohort as applied to the SCI cohort.

Outcomes and comorbidities

Each study participant was followed until a diagnosis of AF, death, loss to follow-up, withdrawal from the NHI program, or December 31, 2011, whichever occurred first.

We used inpatient diagnosis files to determine baseline comorbidities, including diabetes (*ICD-9-CM* code 250), hypertension (*ICD-9-CM* codes 401–405), hyperlipidemia (*ICD-9-CM* code 272), chronic obstructive pulmonary disease (COPD) (*ICD-9-CM* codes 491, 492, and 496), heart failure (*ICD-9-CM* code 428), coronary artery disease (CAD) (*ICD-9-CM* codes 410–414), stroke (*ICD-9-CM* codes 430–438), cancer (*ICD-9-CM* codes 140–241), hyperthyroidism (*ICD-9-CM* code 242), and chemotherapy.

Statistical analysis

We first compared the distributions of sex, age, and baseline comorbidities between the SCI and non-SCI cohorts. Then, the χ^2 test was used to examine categorical variables and the Student *t* test was used to examine continuous variables. The cumulative incidence of AF in the SCI and non-SCI cohorts was assessed using the Kaplan-Meier method, and differences were assessed using a log-rank test. The incidence densities, stratified according to sex, age, and comorbidities, were estimated for both cohorts. The relative risk of developing AF in patients with SCI, compared with the non-SCI cohort, was analyzed using univariate and multivariate Cox proportional hazards regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox models. The multivariate Cox models were adjusted for age, sex, and the comorbidities of diabetes, hypertension, hyperlipidemia, COPD, congestive heart failure (CHF), CAD, stroke, and hyperthyroidism. Further analysis was performed to assess whether AF was associated with the level of SCI. A 2-tailed *P* value of $<.05$ was considered to be statistically significant. All analyses were performed using SAS statistical software version 9.3 for Windows (SAS Institute, Inc., Cary, NC).

Results

This study included 41,691 patients with SCI and 166,764 patients without SCI (Table 1). No statistical difference was observed in the distribution between the SCI and non-SCI cohorts. The SCI cohort was significantly older than the non-SCI cohort (mean age 52.0 ± 18.1 years vs 51.5 ± 18.2 years; $P < .001$). Overall, patients were predominantly men